Summary of Pediatric Clinical Trial Data : Fluticasone and Budesonide

Pediatric Advisory Committee Meeting
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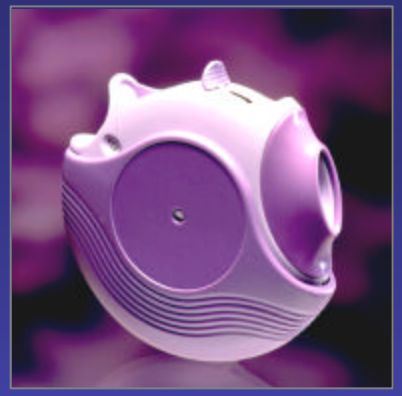
Fluticasone

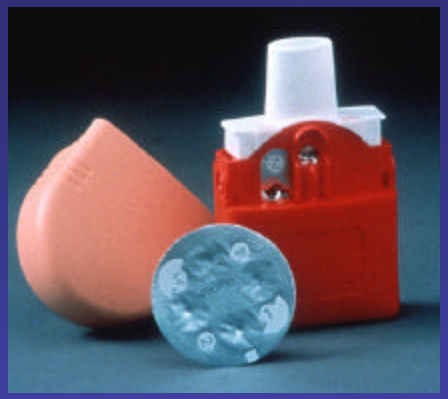
Product	Dosage form	Original Approval	Pediatric Approval
Cutivate® Ointment	Ointment, Topical	12/14/1990	None
Cutivate® Cream	Cream, Topical	12/18/1990	3 months of age or older
Flonase®	Aerosol, Metered; Nasal	10/19/1994	4 years of age and older
Flovent® CFC	Aerosol, Metered; Inhalation	3/27/1996	12 years of age and older
Flovent Rotadisk®	Powder; Inhalation	11/7/1997	4 years of age and older
Advair Diskus®	Powder; Inhalation	8/24/2000	4 years of age and older
Flovent Diskus® (product not marketed)	Powder; Inhalation	9/29/2000	4 years of age and older
Flovent®Aerosol HFA	Aerosol, Metered; Inhalation	5/14/2004	12 years of age and older

Budesonide

Product	Dosage form	Original Approval	Pediatric Approval
Rhinocort® (discontinued)	Aerosol, Metered; Nasal	2/14/1994	6 years of age and older
Pulmicort Turbuhaler®	Powder; Metered Inhalation	6/24/1997	6 years of age and older
Rhinocort Aqua®	Spray, Metered; Nasal	10/01/1999	6 years of age and older
Pulmicort Respules®	Suspension; Inhalation	8/8/2000	1 to 8 years old
Entocort® EC	Capsule; Oral	10/2/2001	No

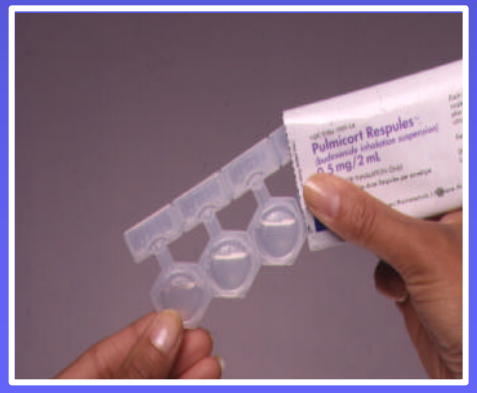


Advair Diskus®



Flovent Rotadisk®

Flovent® MDI



Pulmicort Respules®

Pulmicort Turbuhaler®

Entocort® EC

Nasal Preparations

Flonase®

Rhinocort Aqua®

Pediatric Exclusivity Studies: Fluticasone

- 7 dermatology and pulmonary studies requested
  - 4 studies requested for Cutivate® (dermatology)
  - 1 study for Flonase®
  - 2 studies for Flovent®
- In Vitro Study Report characterizing dose delivery for Flovent® using different U.S. marketed spacers
- Population PK Report for Flovent®

Cutivate® (Fluticasone)

Historical

- Cutivate® cream approved for use in children 3 months of age and older since June 17, 1999
- Written Request for other fluticasone formulations issued on June 25, 1999
  - 3 studies requested for Cutivate® lotion
  - 1 study for Cutivate® ointment
- Advisory Committee held on October 29, 2003-- *Clinical Risk Management of HPA Axis Suppression in Children with Atopic Dermatitis being treated with Topical Corticosteroids*

Present

- Only Cutivate® cream is indicated for pediatric use

Cutivate® Cream (Fluticasone)

•Studies described in label (not requested for pediatric exclusivity)

•43 pediatric patients treated with Cutivate® cream 0.05% for atopic dermatitis over at least 35% of body surface area for 4 weeks

• 2 patients had HPA axis suppression

•Follow up testing available for 1 of the 2 patients demonstrated normally responsive HPA axis

Cutivate® Ointment (Fluticasone)

- Studies requested for exclusivity
- 35 pediatric patients treated with Cutivate® ointment for atopic dermatitis over at least 35% of body surface area for 3-4 weeks
- Subnormal adrenal function observed with cosyntropin stimulation testing in 4 patients
- Recovery of adrenal function unknown
- Information incorporated into pediatric use subsection of labeling
- Cutivate® ointment not indicated for pediatric use

Nursing Mothers: Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when CUTIVATE Ointment is administered to a nursing woman.

Pediatric Use: Use of CUTIVATE Ointment in pediatric patients is not recommended.

In a study of 35 pediatric patients treated with fluticasone propionate ointment, 0.005% for atopic dermatitis over at least 35% of body surface area, subnormal adrenal function was observed with cosyntropin stimulation testing at the end of 3 to 4 weeks of treatment in 4 patients who had normal testing prior to treatment. It is not known if these patients had recovery of adrenal function because follow-up testing was not performed (see PRECAUTIONS: Laboratory Tests and ADVERSE REACTIONS). The decreased responsiveness to cosyntropin testing was not correlated to age of patient, amount of fluticasone propionate ointment used, or serum levels of fluticasone propionate. Plasma fluticasone propionate were not performed in a 6-month-old patient who demonstrated an abnormal response to cosyntropin stimulation testing.

Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing syndrome than mature patients because of a larger skin surface to body weight ratio.

HPA axis suppression, Cushing syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in pediatric patients receiving topical corticosteroids. Manifestations of adrenal suppression in pediatric patients include low plasma cortisol levels and an absence of response to ACTH stimulation.

Fluticasone

Flonase®

Summary of Growth Study: Flonase®

- Study not requested for pediatric exclusivity
- One year multicenter, randomized, double blind, placebo controlled, parallel group, multicenter longitudinal growth study in patients with perennial allergic rhinitis
  - N=150 children
  - Ages: 3-9 years
- Mean reduction in growth velocity after one year of treatment with Flonase® 200 mcg per day was 0.137 cm/yr
- HPA axis evaluation showed no interpretable effects on urinary free cortisol
- Study supports safety in children at the maximum approved dose and twice daily dose typically used in this age group
- Recommendation for results of one-year growth study incorporated in labeling

Pediatric Use: Six hundred fifty (650) patients aged 4 to 11 years and 440 patients aged 12 to 17 years were studied in US clinical trials with fluticasone propionate nasal spray. The safety and effectiveness of FLONASE Nasal Spray in children below 4 years of age have not been established.

Controlled clinical studies have shown that intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with intranasal corticosteroids, including the impact on final adult height, are unknown. The potential for "catch-up" growth following discontinuation of treatment with intranasal corticosteroids has not been adequately studied. The growth of pediatric patients receiving intranasal corticosteroids, including FLONASE Nasal Spray, should be monitored routinely (e.g., via stadiometry). The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained and the risks/benefits of treatment alternatives. To minimize the systemic effects of intranasal corticosteroids, including FLONASE Nasal Spray, each patient should be titrated to the lowest dose that effectively controls his/her symptoms.

A 1-year placebo-controlled clinical growth study was conducted in 150 pediatric patients (ages 3 to 9 years) to assess the effect of FLONASE Nasal Spray (single daily dose of 200 mcg, the maximum approved dose) on growth velocity. From the primary population of 56 patients receiving FLONASE Nasal Spray and 52 receiving placebo, the point estimate for growth velocity with FLONASE Nasal Spray was 0.14 cm/year lower than that noted with placebo (95%

Summary of HPA Axis Study: Flonase®

- Study requested for pediatric exclusivity

- 6 week multicenter, randomized, double blind, placebo controlled, parallel group HPA axis study in patients with allergic rhinitis
  - N=65
  - Ages: 2-<4 years
- Evaluation of 12-hour urinary free cortisol
- Despite limitations presented by difficulties in urine collection, results tend to support conclusion that there are no significant effects of 6-weeks of Flonase® on HPA axis in this age group

Fluticasone

Flovent® CFC MDI

Pediatric Exclusivity Studies: Fluticasone®

- 7 dermatology and pulmonary studies requested
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In Vitro Study Report

- Study requested for pediatric exclusivity
- Comparison of the particle size distribution by cascade impaction for Flovent® CFC MDI with and without use of various spacers:
  - Aerochamber® -Optichamber®
  - Aerochamber Plus™
- Results appear to indicate that the in vitro respirable particle content similar to when MDI studied alone or with either of the 3 spacers
- Study was unable to evaluate factors important to the *in vivo* clinical setting

Summary of Efficacy/Safety Studies: Flovent®

- Studies requested for pediatric exclusivity
- 2 trials, 12-week, randomized, parallel group, double-blind, placebo-controlled efficacy and safety studies in children with symptomatic asthma
  - N=211 -N=332
  - Ages: 6-23 months -Ages: 24-47 months
- Detectable plasma levels of fluticasone seen in 13 placebo treated patients. Impossible to evaluate extent actual patient exposure.
- PK/PD relationship difficult to assess
- Interpretation: Impossible to determine whether studies derived an accurate assessment of safety or efficacy
- No label change resulted

Pediatric Exclusivity Studies: Budesonide

- 2 studies requested
  - Safety of budesonide nebulizing suspension for treatment of asthma in children 6 months-1 year
  - HPA-axis safety study of budesonide nasal spray in children 2-6 years

Budesonide

Rhinocort Aqua®

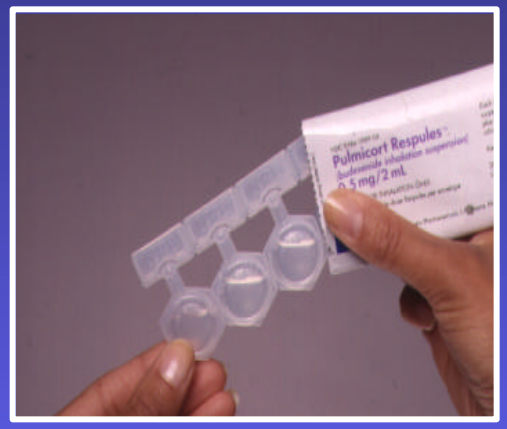
Summary of Safety Study: Budesonide

- Study requested for pediatric exclusivity
- 6 week multicenter randomized, double-blind placebo-controlled study to evaluate the effect of Rhinocort Aqua® on HPA axis in patients with allergic rhinitis

  - N=78
  - Ages: 2- < 6 years

- HPA axis function evaluated by low dose cosyntropin stimulated plasma cortisol measurements at baseline and following 6 weeks treatment
- No suppressive effect on HPA-axis observed in this study

Budesonide



Pulmicort® Respules

Summary of Safety Study: Budesonide

- Study requested for pediatric exclusivity
- 12-week, randomized, double-blind, placebo-controlled study to evaluate safety of Pulmicort Respules® 0.5mg and 1.0 mg daily compared to placebo in pediatric patients with mild to moderate asthma or recurrent/persistent wheezing
  - N=141
  - Ages: 6-12 months
- Main safety concerns:

  -HPA axis suppression: cortisol level <500 nmol/L (<18 ug/dl) 60 minutes post-ACTH stimulation

  -suppression of linear growth: growth velocity by crown-heel length

Summary of Safety Study: Budesonide

- **HPA axis suppression:**

Placebo	: 3% (1/31)
Pulmicort Respules 0.5 mg/day	: 14% (4/28)
Pulmicort Respules 1.0 mg/day	: 12% (2/17)

- **Suppression of linear growth: mean growth velocity**

	Result	Delta	95%CI
Placebo	: 3.7 cm		
Pulmicort Respules 0.5 mg/day	: 3.5 cm	-0.2 cm	(-0.6, 1.0)
Pulmicort Respules 1.0 mg/day	: 3.1 cm	-0.6 cm	(-0.2, 1.4)

The effects of PULMICORT RESPULES on the hypothalamic-pituitary-adrenal (HPA) axis were studied in three, 12-week, double-blind, placebo-controlled studies in 293 pediatric patients, 6 months to 8 years of age, with persistent asthma. For most patients, the ability to increase cortisol production in response to stress, as assessed by the short cosyntropin (ACTH) stimulation test, remained intact with PULMICORT RESPULES treatment at recommended doses. In the subgroup of children age 6 months to 2 years (n=21) receiving a total daily dose of PULMICORT RESPULES equivalent to 0.25 mg (n=5), 0.5 mg (n=5), 1 mg (n=8), or placebo (n=3), the mean change from baseline in ACTH-stimulated cortisol levels showed a decline in peak stimulated cortisol at 12 weeks compared to an increase in the placebo group. These mean differences were not statistically significant compared to placebo. Another 12-week study in 141 pediatric patients 6 to 12 months of age with mild to moderate asthma or recurrent/persistent wheezing was conducted. All patients were randomized to receive either 0.5 mg or 1 mg of PULMICORT RESPULES or placebo once daily. A total of 28, 17, and 31 patients in the PULMICORT RESPULES 0.5 mg, 1 mg, and placebo arms respectively, had an evaluation of serum cortisol levels post-ACTH stimulation both at baseline and at the end of the study. The mean change from baseline to Week 12 ACTH-stimulated minus basal plasma cortisol levels did not indicate adrenal suppression in patients treated with PULMICORT RESPULES versus placebo. However, 7 patients in this study (4 of whom received PULMICORT RESPULES 0.5 mg, 2 of whom received PULMICORT RESPULES 1 mg and 1 of whom received placebo) showed a shift from normal baseline stimulated cortisol level (≥500 nmol/L) to a subnormal level (<500 nmol/L) at Week 12. In 4 of these patients receiving PULMICORT RESPULES, the cortisol values were near the cutoff value of 500 nmol/L.

Summary

- Studies for pediatric exclusivity resulted in labeling changes for fluticasone and budesonide containing products
- Pediatric trials for fluticasone and budesonide have identified important safety concerns which have been incorporated into labeling